

-47-

What is claimed is:

### CLAIMS

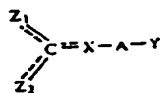
1. A method for treating a subject afflicted with a nervous system disease  
5 comprising

administering to the subject an amount of creatine, creatine phosphate or a creatine analog or a salt thereof compound sufficient to prevent, reduce, ameliorate or eliminate said disease.

2. The method of claim 1 wherein the subject is a mammal.  
10 3. The method of claim 1 wherein the subject is human.

4. A method for treating a subject for diseases of the nervous system comprising:

administering an effective amount of a creatine compound to a subject such that the subject is treated for diseases of the nervous system, wherein the  
15 creatine compound is of the general formula:



and pharmaceutically acceptable salts thereof, wherein:

- a) Y is selected from the group consisting of:  $-\text{CO}_2\text{H}$ ,  $-\text{NHOH}$ ,  $-\text{NO}_2$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{C}(=\text{O})\text{NHSO}_2\text{J}$  and  $-\text{P}(=\text{O})(\text{OH})(\text{OJ})$ , wherein J is selected from the

-48-

group consisting of: hydrogen, C<sub>1</sub>-C<sub>6</sub> straight chain alkyl, C<sub>3</sub>-C<sub>6</sub> branched alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> branched alkenyl, and aryl;

5 b) A is selected from the group consisting of: C, CH, C<sub>1</sub>-C<sub>5</sub>alkyl, C<sub>2</sub>-C<sub>5</sub>alkenyl, C<sub>2</sub>-C<sub>5</sub>alkynyl, and C<sub>1</sub>-C<sub>5</sub> alkoyl chain, each having 0-2 substituents which are selected independently from the group consisting of:

10 1) K, where K is selected from the group consisting of: C<sub>1</sub>-C<sub>6</sub> straight alkyl, C<sub>2</sub>-C<sub>6</sub> straight alkenyl, C<sub>1</sub>-C<sub>6</sub> straight alkoyl, C<sub>3</sub>-C<sub>6</sub> branched alkyl, C<sub>3</sub>-C<sub>6</sub> branched alkenyl, and C<sub>4</sub>-C<sub>6</sub> branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

15 2) an aryl group selected from the group consisting of: a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: -CH<sub>2</sub>L and -COCH<sub>2</sub>L where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy; and

3) -NH-M, wherein M is selected from the group consisting of: hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>1</sub>-C<sub>4</sub> alkoyl, C<sub>3</sub>-C<sub>4</sub> branched alkyl, C<sub>3</sub>-C<sub>4</sub> branched alkenyl, and C<sub>4</sub> branched alkoyl;

20 c) X is selected from the group consisting of NR<sub>1</sub>, CHR<sub>1</sub>, CR<sub>1</sub>, O and S, wherein R<sub>1</sub> is selected from the group consisting of:

1) hydrogen;

2) K where K is selected from the group consisting of: C<sub>1</sub>-C<sub>6</sub> straight alkyl, C<sub>2</sub>-C<sub>6</sub> straight alkenyl, C<sub>1</sub>-C<sub>6</sub> straight alkoyl, C<sub>3</sub>-C<sub>6</sub> branched alkyl, C<sub>3</sub>-C<sub>6</sub> branched alkenyl, and C<sub>4</sub>-C<sub>6</sub> branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

3) an aryl group selected from the group consisting of a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: -CH<sub>2</sub>L and -COCH<sub>2</sub>L where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

4) a C<sub>5</sub>-C<sub>9</sub> α-amino-ω-methyl-ω-adenosylcarboxylic acid attached via the ω-methyl carbon;

5) a C<sub>5</sub>-C<sub>9</sub> α-amino-ω-aza-ω-methyl-ω-adenosylcarboxylic acid attached via the ω-methyl carbon; and

6) a C<sub>5</sub>-C<sub>9</sub> α-amino-ω-thia-ω-methyl-ω-adenosylcarboxylic acid attached via the ω-methyl carbon;

d) Z<sub>1</sub> and Z<sub>2</sub> are chosen independently from the group consisting of: =O, -NHR<sub>2</sub>, -CH<sub>2</sub>R<sub>2</sub>, -NR<sub>2</sub>OH; wherein Z<sub>1</sub> and Z<sub>2</sub> may not both be =O and wherein R<sub>2</sub> is selected from the group consisting of:

1) hydrogen;

2) K, where K is selected from the group consisting of: C<sub>1</sub>-C<sub>6</sub> straight alkyl; C<sub>2</sub>-C<sub>6</sub> straight alkenyl, C<sub>1</sub>-C<sub>6</sub> straight alkoyl, C<sub>3</sub>-C<sub>6</sub> branched

-50-

alkyl, C<sub>3</sub>-C<sub>6</sub> branched alkenyl, and C<sub>4</sub>-C<sub>6</sub> branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

5           3)    an aryl group selected from the group consisting of a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: -CH<sub>2</sub>L and -COCH<sub>2</sub>L where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

4)    a C<sub>4</sub>-C<sub>8</sub> α-amino-carboxylic acid attached via the α-carbon;

10           5)    B, wherein B is selected from the group consisting of: -CO<sub>2</sub>H, -NHOH, -SO<sub>3</sub>H, -NO<sub>2</sub>, OP(=O)(OH)(OJ) and -P(=O)(OH)(OJ), wherein J is selected from the group consisting of: hydrogen, C<sub>1</sub>-C<sub>6</sub> straight alkyl, C<sub>3</sub>-C<sub>6</sub> branched alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> branched alkenyl, and aryl, wherein B is optionally connected to the nitrogen via a linker selected from the group  
15           consisting of: C<sub>1</sub>-C<sub>2</sub> alkyl, C<sub>2</sub> alkenyl, and C<sub>1</sub>-C<sub>2</sub> alkoyl;

6)    -D-E, wherein D is selected from the group consisting of: C<sub>1</sub>-C<sub>3</sub> straight alkyl, C<sub>3</sub> branched alkyl, C<sub>2</sub>-C<sub>3</sub> straight alkenyl, C<sub>3</sub> branched alkenyl, C<sub>1</sub>-C<sub>3</sub> straight alkoyl, aryl and aroyl; and E is selected from the group consisting of: -(PO<sub>3</sub>)<sub>n</sub>NMP, where n is 0-2 and NMP is ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; -[P(=O)(OCH<sub>3</sub>)(O)]<sub>m</sub>-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; -  
20           [P(=O)(OH)(CH<sub>2</sub>)]<sub>m</sub>-Q, where m is 0-3 and Q is a ribonucleoside connected

-51-

via the ribose or the aromatic ring of the base; and an aryl group containing 0-3 substituents chosen independently from the group consisting of: Cl, Br, epoxy, acetoxy, -OG, -C(=O)G, and -CO<sub>2</sub>G, where G is independently selected from the group consisting of: C<sub>1</sub>-C<sub>6</sub> straight alkyl, C<sub>2</sub>-C<sub>6</sub> straight alkenyl, C<sub>1</sub>-C<sub>6</sub> straight alkoyl, C<sub>3</sub>-C<sub>6</sub> branched alkyl, C<sub>3</sub>-C<sub>6</sub> branched alkenyl, C<sub>4</sub>-C<sub>6</sub> branched alkoyl, wherein E may be attached to any point to D, and if D is alkyl or alkenyl, D may be connected at either or both ends by an amide linkage; and

7) -E, wherein E is selected from the group consisting of - (PO<sub>3</sub>)<sub>n</sub>NMP, where n is 0-2 and NMP is a ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; -[P(=O)(OCH<sub>3</sub>)(O)]<sub>m</sub>-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; -[P(=O)(OH)(CH<sub>2</sub>)]<sub>m</sub>-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; and an aryl group containing 0-3 substituents chosen independently from the group consisting of: Cl, Br, epoxy, acetoxy, -OG, -C(=O)G, and -CO<sub>2</sub>G, where G is independently selected from the group consisting of: C<sub>1</sub>-C<sub>6</sub> straight alkyl, C<sub>2</sub>-C<sub>6</sub> straight alkenyl, C<sub>1</sub>-C<sub>6</sub> straight alkoyl, C<sub>3</sub>-C<sub>6</sub> branched alkyl, C<sub>3</sub>-C<sub>6</sub> branched alkenyl, C<sub>4</sub>-C<sub>6</sub> branched alkoyl; and if E is aryl, E may be connected by an amide linkage;

e) if R<sub>1</sub> and at least one R<sub>2</sub> group are present, R<sub>1</sub> may be connected by a single or double bond to an R<sub>2</sub> group to form a cycle of 5 to 7 members;

f) if two R<sub>2</sub> groups are present, they may be connected by a single or a double bond to form a cycle of 4 to 7 members; and

-52-

g) if  $R_1$  is present and  $Z_1$  or  $Z_2$  is selected from the group consisting of  $-NHR_2$ ,  $-CH_2R_2$  and  $-NR_2OH$ , then  $R_1$  may be connected by a single or double bond to the carbon or nitrogen of either  $Z_1$  or  $Z_2$  to form a cycle of 4 to 7 members.

- 5 5. The method of claim 4 wherein the treatment comprises reducing or eliminating symptoms associated with a preexisting disease of the nervous system.
6. The method of claim 4 wherein the treatment comprises preventing the occurrence of diseases of the nervous system within the subject.
- 10 7. The method of claim 4 wherein the creatine compound is creatine.
8. The method of claim 4 wherein the creatine compound is creatine phosphate.
9. The method of claim 4 wherein the creatine compound is cyclocreatine.
10. The method of claim 4 wherein the creatine compound is cyclocreatine phosphate.
- 15 11. The method of claim 4 wherein the creatine compound is homocyclocreatine.
12. The method of claim 4 wherein the disease of the nervous system is selected from the groups consisting of neuropathies; Alzheimer disease, Parkinson's disease, Huntington's disease, motor neuron disease, traumatic nerve injury, multiple sclerosis, acute disseminated encephalomyelitis, acute necrotizing hemorrhagic leukoencephalitis, dysmyelination disease, mitochondrial disease, 20 migrainous disorder, bacterial infection, fungal infection, stroke, aging,

dementia, peripheral nervous system diseases and mental disorders such as depression and schizophrenia.

13. The method of claim 12 wherein the creatine compound is selected from the group consisting of creatine, creatine phosphate, cyclocreatine and cyclocreatine phosphate.
14. The method of claim 4 further comprising coadministering to the subject a neurotransmitter, a neurotransmitter analog, a steroid, an immunomodulating agent, or an immune suppressive agent.
15. The method of claim 4 wherein the subject is treated for diseases of the nervous system by reducing or eliminating symptoms associated with a preexisting diseases of the nervous system.
16. The method of claim 4 wherein the subject is treated for diseases of the nervous system by preventing the occurrence of a disease of the nervous system within the subject.
17. A method for alleviating in a subject being treated for a nervous system disease toxic side effects of drugs used to treat the nervous system diseases, comprising administering to the subject an amount of a creatine, creatine phosphate or a creatine analog, or a salt thereof, sufficient to prevent, reduce, ameliorate or alleviate said toxic side effects.
18. The method of claim 17 wherein the creatine analog is cyclocreatine or cyclocreatine phosphate.